Atty. Docket No.: 11111/1210 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Segal	Examiner:	Belyavskyi, M.
Serial No.:	09/318,870		
Filed:	May 26, 1999	Group Art Unit:	1644
Titled:	Cytokine Coated Cells and Methods for Modulating an Immune Response to an Antigen	Conf. No.:	2018

CERTIFICATE OF MAILING UNDER 37 CFR 1.10

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Nancy Arsenault
Name of Person Mailing

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Mail Stop Appeal Brief - Patent
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Alexandria, VA 22313-1450

RESPONSE TO NOTIFICATION OF NON-COMPLIANCE WITH 37 CFR 1.192(c)

Sir:

This is filed in response to the Notification of Non-Compliance with 37 CFR 1.192(c) mailed May 25, 2004.

1. The Notice stated that Appellant has improperly introduced a new reference (Pardoll, D) that is not of record into Appeal Brief.

Applicant has amended the Appeal Brief to remove reference to (Pardoll, D).

2. The Notice stated that there is no arguments under Grouping of Claims and Argument items of the Appeal Brief why the claims subject to the same rejection are separately patentable.

Applicant has amended the Appeal Brief to include this argument.

Respectfully submitted,

Date: June 25, 2004

Barbara A. Hayne (34,614) for Kathleen Williams

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06-28-04

AF/ 1644

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TRANSMITTAL LETTER

Enclosed for filing in the above-identified patent application, please find the following documents:

1. Response to Notice of Non-Compliance with 37 CFR 1.192(c);
2. Appeal Brief in triplicate; and
3. Return Post Card.

The Commissioner for Patents is hereby authorized to charge any additional fees or credit any overpayment in the total fees to Deposit Account No. 16-0085, Reference No. 11111/1210. A duplicate of this transmittal letter is enclosed for this purpose.

Respectfully submitted,

Date: June 25, 2004

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Nancy Arsenault
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P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF UNDER 37 C.F.R. §1.192

Sir:

This Appeal Brief is submitted pursuant to the Notice of Appeal, mailed January 30, 2004, from the Examiner's final rejection of claims 1-8, 13, 14, 17-20, and 22-25, mailed January 8, 2004 in the above-referenced application.

Applicants also submit concurrently herewith, an After Final amendment to the claims, which Applicant believes, when taken in combination with the arguments of record and the submissions below, place the claims in condition for allowance.

Each of the requirements set forth in 37 C.F.R. § 1.192(c) follow under separate headings.

Real Party in Interest

The real party in interest in the above captioned patent application is the assignee, Genitrix, LLC, by virtue of an assignment document dated 6/30/99, and recorded at Reel: 010074, Frame: 0546.

Related Appeals and Interferences

There are no related appeals or interferences in this case.

Status of Claims

Claims 1-8, 13, 14, 17-20, and 22-25 stand finally rejected and are the subject of this appeal. A copy of these claims can be found in Appendix I, attached. They do not reflect the proposed amendments as set forth in the Amendment After Final Rejection submitted herewith. Claims 9-12, 15, 16, and 21 are cancelled.

Status of Amendments

The Amendment After Final Rejection filed herewith has not been entered. Therefore, the claims which are the subject of this Appeal Brief do not reflect the amendments set forth in the Amendment After Final Rejection. Applicants arguments below, however, refer to the suggested amendments to the claims as indicated in the Amendment After Final Rejection.

Summary of the Invention

The invention is based, in part, on the discovery that cytokine-coated cells, that is cells which have been modified in such a way as to bear a cell-surface associated cytokine, wherein the cytokine is exogenous to the cell, modulate the immune response in the recipient to an antigen or antigens contained in or attached to the cells. Thus, the present invention provides a method for the modulation of the immune response of, or vaccination of an animal, preferably a mammal, to an antigen by administering to the animal a vaccine composition comprising a cytokine-coated cell which comprises the antigen, and wherein the cytokine of the cytokine-coated cells is exogenous to the cell (page 4, lines 15-20). The method of the invention may be further enhanced by the inclusion of an opsonin-enhanced cell in the vaccine composition to be administered to an animal (page 4, lines 24-29). In one embodiment of the invention, the

cytokine of the cytokine-coated cell is a ligand for the GM-CSF receptor, or is a ligand for one of the receptors selected from the group of the IL-2 receptor, the IL-4 receptor, the IL-6 receptor, the IL-10 receptor, the IL-12 receptor, the TNF-α receptor, the IFN-γ receptor, and a chemokine receptor (page 6, lines 5-6).

Applicant submits that it is highly advantageous to use a cytokine that is attached to the antigen-containing cell because it directly facilitates interactions of the cell with host immune system cells, e.g. uptake of the cell (and its antigens) by host APCs. Moreover, the use of an exogenous cytokine, i.e. one that can attach to the cell from outside, is a critical advance over the endogenous expression of heterologous, transmembrane cytokines by genetic modification (e.g., as taught by Hiserodt et al. described below). The latter is highly technically difficult and time-consuming, and sometimes not possible at all; methods for genetic transduction of cells are often inefficient and labor intensive. The most efficient transduction methods use viral vectors, which present safety problems in preparing vaccines for use in humans or other animals. The use of an exogenous, engineered cytokine instead, without genetic manipulation of the vaccine cell, circumvents and therefore solves all of these problems.

Issues

1. Whether claims 1-8, 13, 14, 17-20, and 22-25 are unpatentable as being based on a non-enabling disclosure.

2. Whether claims 1, 2, 13, 14, 17-19, and 22-25 are unpatentable as being anticipated under 35 U.S.C. §102(e) by Hiserodt et al. (U.S. Pat. No. 6,277,368).

3. Whether claims 3-8 and 20 are unpatentable as being obvious under 35 U.S.C. §103(a) over the combined teachings of Hiserodt et al. and the "Known fact" disclosed in the specification on pages 52-54 and 66-68.

Grouping of Claims

The claims do not stand or fall together with regards to the rejection under 35 U.S.C. § 112, first paragraph, 35 U.S.C. § 102(e), or 35 U.S.C. §103(a). The claims under appeal may be

grouped as follows: Group I: Claims 1, 3-8, 17-20, and 22-25; Group II: Claim 2 and 3-8; Group III: Claim 13 and 14; and Group IV: Claim 15 and 16. Applicants arguments in support of this assertion are provided below.

Argument

Argument in Support of Claim Grouping

Applicant submits that the claims of each group are separately patentable over the claims of the other groups as the independent claim of each group contains elements which render the claims of each group novel and patentably distinct over the other groups. Specifically, although each of independent claim 1 (Group I) claims 2, (Group II), claim 13 (Group III), and claim 15 (Group IV) are directed to a method of vaccinating a mammal to a selected antigen by administering a cytokine coated cell comprising the antigen, wherein the cytokine is exogenous to the cell, each of these claims recite distinct cytokines. For example, claim 2 requires that the cytokine be an engineered cytokine according to the definitions of the invention; claim 13 requires that the cytokine be a ligand for the GM-CSF receptor; and claim 15 recites that the cytokine be a ligand for a specific receptor. Claim 1 broadly recites that the cytokine be exogenous. Since each of the independent claims (2, 13, and 15) require structurally distinct cytokines having unique properties, the claims are patentably distinct. Although the claims are, according to the previous Office Actions, all subject to the same rejection under 35 U.S.C. §112, first paragraph, the enablement rejection which relates, in part, to the use of a cytokine according to the invention, is fundamentally different for each of the grouped claims because the claims of each group contain structurally distinct cytokines. Likewise, the rejections of the distinct groups of claims under both 35 U.S.C. §102(e) and §103(a) are fundamentally distinct as the claims encompassed by each group comprise structurally distinct cytokines. Hence, the Groups comprising these independent claims are separately patentable, and the claims do not rise or fall together.

Rejection of Claims 1-8, 13, 14, 17-20, and 22-25 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected the claims as not being enabled for "*vaccinating* a mammal to *any* antigen, comprising administering to a mammal *any* vaccine comprising *any* cytokine coated cell comprising said antigen". Applicants respectfully disagree.

The claims are enabled for vaccination

The Examiners rejection is based, in part, on the Examiner's definition of the term "vaccinate". The Examiner has defined a "vaccine" as "a composition to induce a specific immunity that **prevent** or **protect** against a specific disease caused by a specific agent". The Examiner asserts that the specification is thus not enabling because the specification does not provide information on the immunogenicity of any vaccine comprising any cytokine-coated cell comprising antigen or the ability of such to "protect or prevent from antigen-specific disease". In other words, the Examiner is reading a *100% protective immunity* limitation into the claims based on selective extrinsic evidence, which limitation is inconsistent with the definition provided by the specification.

Applicant submits that the Examiner is erroneously confusing the enablement requirement with the requirement for claim definiteness. The term "vaccinate" is defined in the specification. Applicant has defined the term "vaccinate" as the modulation of an immune response to an antigen (page 9, lines 21-22). More specifically, the specification defines "vaccinating" as the modulation of an immune response to an antigen such that "the response is between about 5 and 100%...more or less efficient, more or less rapid, greater or lesser in magnitude, and/or more or less easily induced" (page 9, line 26 – page 10, line 1). Moreover, as described above, Applicant has provided extensive teachings as to how one of skill in the art would determine the modulation of an immune response, including assaying for tumor rejection. The specification teaches on page 89, lines 12-19 that if survival or tumor onset in an animal to which has been administered a cytokine-coated cell of the invention differs from a control animal, then immunomodulation has occurred. More specifically, the specification teaches that if at least 10% of the animals in the test group survive 100% longer than the mean survival in the control group, the test is positive, or alternatively, if onset of tumors in 20% of the test animals is 50% later than mean onset in the control animals, the test is positive (i.e., animals are

vaccinated). Thus, the meaning of "vaccinate" is clear from the specification and the claims thus clearly set forth the area over which Applicant seeks exclusive rights. The enablement requirement means that the specification must describe the manner of making and using the invention in such clear terms as to enable any person skilled in the art to make and use it. The specification clearly teaches how to perform the vaccination method in a mammal as recited in the claims (this is discussed further below).

Because the term "vaccinate" is clear and unambiguous (i.e., definite), the Examiner has improperly relied on extrinsic evidence to support a different interpretation, and to thus improperly read a limitation (i.e., "protective immunity") into the claims. The Examiner asserts that the meaning of "vaccinate" requires prevention of disease. The Examiner's definition is inconsistent with Applicant's specification-defined definition. Applicant submits that the Examiner, in using his own definition of vaccinate, is improperly importing extrinsic evidence into the prosecution record. The law is clear that the specification may use words in a manner which is inconsistent with the meaning reflected, for example, in a dictionary definition. In such a case, the inconsistent dictionary definition must be rejected [See, e.g., *Reinshaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243 (Fed. Cir. 1998)] ("[A] common meaning, such as one expressed in a relevant dictionary, that flies in the face of the patent disclosure is undeserving of fealty"). Thus, the law supports the conclusion that the presumption in favor of a dictionary definition will be overcome where the patentee, acting as his or her own lexicographer, has clearly set forth an explicit definition of the term. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994); *Intellicall, Inc. v. Phonometrics, Inc.*, 952 F.2d 1384, 1387-88 (Fed. Cir. 1992). This is the case in the instant specification and claims.

Applicant submits that the law expressly gives Applicant the ability to define terms in the claims according to Applicant's wishes, provided that such definition is not "repugnant" to the meaning normally accorded such a term in the art. *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947); *Multiform Desiccants Inc. v. Medzam Ltd.*, 133 F.3d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998). Applicant submits that defining "vaccinate" according to the invention to mean a range of immune responses to a vaccine composition (from 5% to full prevention) is not repugnant to the meaning of "vaccinate". The Examiner has asserted in the

Final Rejection that "by definition, a vaccine is a composition to induce a specific immunity that prevent or protect against a specific disease caused by a specific agent", although the Examiner provides no citation or basis for this definition. Applicant submits that the meaning of the term "vaccinate" as defined in the specification is not repugnant to the usual meaning of the term. Applicant submits that Dorland's Illustrated Medical Dictionary (1985, 26th Ed., W.B. Saunders Co., Philadelphia) defines "vaccinate" as "to inoculate with a vaccine for the purpose of producing immunity", and further defines "immunity" as "**heightened** responsiveness to antigenic challenge that leads to **more rapid** binding or elimination of antigen than in the nonimmune state". Thus, Applicant submits that the definition of "vaccinate" in the specification as being at least a 5% increase in an immune response up to full prevention of disease is consistent with the understood meaning in the art of the term "vaccinate".

As submitted by Applicant in the telephone interview of November 5, 2003, however, whether the Examiner, as required, accords the term vaccinate with Applicant's definition, or gives the term his own meaning, Applicant has enabled the claims of the invention. The working example provided in the specification demonstrates a reduction in tumor formation which falls under Applicant's definition of "vaccinate". For example, Example 7 teaches that after vaccination with cytokine-coated (GM-CSF-GPI-coated) B16 cells, mice (n=5) had a maximum survival period of 32 days. In contrast, control mice (n=4; administered the B16 cells in the absence of GM-CSF-GPI) had a mean survival time of 16 days. As described above, the specification teaches that vaccination is achieved where the response is between about 5 and 100%...more or less efficient, more or less rapid, greater or lesser in magnitude, and/or more or less easily induced, and further teaches that animals are vaccinated if at least 10% of the animals in the test group survive 100% longer than the mean survival in the control group. As shown in Example 7, 20% of the test group had a survival time which was 100% greater than the mean survival of the control group (1 animal in 5 (i.e., 20%) had a 32 day survival time relative to the mean 16 day survival time in controls). In addition, Example 8 in the specification, although prophetic, teaches vaccination of mice with cytokine coated cells wherein at day 60 after the challenge step, "at least 20% or more of the mice that received GPI-GMCSF coated cells will be alive as compared to control mice". The Rule 132 Declaration filed by Dr. Andrew Segal on February 28, 2003 ("the first Segal declaration") gives a working example of the method

described in Example 8. The first Segal declaration teaches that of mice vaccinated with GM-CSF-GPI cytokine coated cells (fibrosarcoma cells), 60-80% of the vaccinated mice did not show development of tumors for 70 days. That is, the vaccine composition of the invention *prevented* tumor formation in 60-80% of treated animals, and moreover, these results fall within the description of "vaccination" provided in Example 8. Further, the Rule 132 Declaration by Dr. Andrew Segal filed with the Amendment After Final Rejection submitted herewith ("the second Segal declaration") demonstrates that 100% of mice which received vaccination with a cytokine-coated vaccine (GM-CSF-HA-coated CMS-5 fibrosarcoma cells) were tumor-free after 40 days, compared to control animals who developed tumors by day 18. That is, the vaccine composition *prevented* tumor growth in all animals to which it was administered. The second Segal declaration also shows that of mice vaccinated with K1735 melanoma cells coated with GM-CSF-HA, 70% were tumor free after more than two months, whereas all control animals had developed tumors in the same time period. That is, the vaccine composition *prevented* tumor growth in 70% of animals to which it was administered. The second Segal declaration also shows that in mice vaccinated with B16F10 murine melanoma cells coated with GM-CSF, an average of 97.5% of metastases to the lungs of the test animals were *prevented.* Similarly, the second Segal declaration shows that lung metastases in a CT26 murine colon carcinoma model were reduced by approximately 45% following vaccination with GM-CSF coated CT26 cells. That is, the method of the invention *prevented* 45% of lung carcinoma metastases compared to control. The Examiner appears to have cited Applicant's statement that the vaccine compositions of the invention are able to prevent tumor formation as support of his contention that "vaccinate" necessitates prevention, but yet still maintains that the claims are not enabled for prevention of disease. This is somewhat confusing. Applicant has taken the position that the specification has provided a definition of vaccinate which includes both total and partial prevention (i.e., modulation of an immune response), but also provides data showing that, even if the term vaccinate is taken to require prevention, then the claims are nonetheless enabled.

In summary, between the specification and Declarations by Dr. Andrew Segal, Applicant has provided six specific working examples of vaccine compositions which fall under the claims of the invention both in the reduction or prevention of primary tumor formation, and/or the reduction or prevention of metasteses. Thus, regardless of whether "vaccinate" is defined

according to the specification or according to the Examiner, the specification is enabling for a method of vaccinating an animal, as claimed. Applicant submits that the data taught in both the Segal declarations is provided in additional support of the vaccination methods already described and supported in the specification, and does not constitute new matter.

(Nevertheless, in order to inspire more economical prosecution of this case, Applicant proposes an alternative to this appeal, i.e., to amend the claims to recite "A method of modulating an immune response in a mammal to a selected antigen..." The Examiner has implied in the Final Rejection that such claim language may overcome the outstanding rejection. Accordingly, as an alternative to this appeal, the Amendment After Final Rejection, submitted herewith, includes an amendment to the claims to replace the term "vaccinate" with the phrase "modulating an immune response in a mammal". Applicant understands that the arguments made herein must be directed to the claims as they stand prior to the entry of the proposed After Final amendment, but where appropriate, have indicated the relevance of Applicant's asserted position with respect to the proposed amended claims should the amendment be entered by the Examiner.)

The claims are enabled for the full scope of vaccination with cytokine

With respect to the Examiner's assertion that the claims are not enabled for vaccinating a mammal to *any* antigen, comprising administering to a mammal *any* vaccine comprising *any* cytokine coated cell comprising said antigen, the Examiner has previously acknowledged that the specification provided a list of cytokines which would function to bring the cytokine coated cell into contact with a leukocyte. Consistent with the teachings in the specification, the state of the art supports Applicant's assertion that a wide range of cytokines can modulate an immune response to an antigen. As demonstrated by the data in the Segal Declarations, the present invention provides a novel and superior mechanism for the efficient, effective delivery of cytokines to modulate an immune response to an antigen, via the use of exogenous cytokines that can attach to cells. The specification provides extensive teachings on the types of cytokines which are useful in the present invention to stimulate the vaccination and modulation of the immune response of an animal to an antigen (discussion of cytokines useful in the invention is

provided below). Therefore applicant submits that the specification is enabling for the claimed method, and provides sufficient teachings to permit one of skill in the art to practice the invention using the full scope of cytokines as recited in the claims.

The specification is enabled for vaccination against antigen

The Examiner has maintained that the specification was not enabled for *any* antigen, particularly in view of the teachings of several publications which reflected the state of the art which existed years prior to Applicant's invention, and which suggested that vaccination of the type claimed was unpredictable (The Examiner cites Ellis (Chapter 29 of Vaccines), Chandrasheker et al. (U.S. Pat. No. 6,248,329), Spitler (Cancer Biotherapy), and Ezzell (NIH Research), all of which were discussed in Applicant's response of October 22, 2003). The Examiner asserts that the specification is not enabled for vaccination against *any* antigen using the cytokine-coated cells of the invention. Applicants respectfully disagree with the Examiner.

As Applicant described in the November 5, 2003 telephone interview, one advantage of the present invention is that upon administration of the vaccine composition of the invention to a mammal, the mammal's immune system is presented with **all** of the antigens which are present in or on the cytokine coated cell. It is thus, not necessary that one of skill in the art know the specific antigens present in the cell (i.e., which epitope of the vaccine the mammal is reacting to) in order to successfully practice the invention. It therefore also provides an opportunity to elicit an immune response against multiple antigens in a cell, regardless of whether the identity of any of those antigens is known. Furthermore, whole cells may be used as a substrate in assays to determine whether an immune response to an antigen contained in the cells has been modulated, so that the identity of a specific antigen need not be known in order to demonstrate the successful practice of the invention.

Applicant submits that an antigen, by definition, is capable, at least when delivered by the methods of the invention, of eliciting an immune response. Applicant also submits that the immune response to an antigen generally arises from the same set of mechanisms, regardless of the origin of the antigen. Thus, for example, immune responses to the MAGE-1 melanoma tumor antigen, the herpes simplex glycoprotein D viral antigen, and the diptheria toxoid bacterial

antigen all result from uptake of the respective antigen by antigen presenting cells, intracellular processing of the respective antigens into short peptides, and presentation of these peptides by APCs to T cells, with activation and expansion of these T cells. Applicant therefore submits that the state of the art supports the expectation that if one or several antigens are operative according to the invention, that many will be, thereby providing enablement for the full scope of the claims. Applicant submits that they have provided evidence that the invention is operative for at least three different types of antigens, and thus provides enablement sufficient to support the full scope of the claimed invention.

The specification provides sufficient enabling disclosure

Applicant submits that to satisfy the enablement requirement, the specification must provide sufficient teaching to permit one of skill in the art to practice the invention, including making a determination of whether a specific species of the invention is operable, without undue experimentation. While the Examiner asserts that the specification is not enabling for each and every possible embodiment of the invention (e.g., the Examiner asserts that all antigens derived from pathogens may not be successful in vaccinating a mammal), Applicant submits that this is irrelevant. The courts have long held that non-operative embodiments are permissible, and are not fatal to a finding of enablement. Applicants respectfully refer the Examiner to *Ex parte Mark* (12 U.S.P.Q.2d 1904 (Bd. Pat. App. & Int. 1989). In this case, the broadest appealed claim was as follows:

> 1. A synthetic mutein of a biologically active native protein in which the native protein has at least one cysteine residue that is free to form a disulfide link and is nonessential to said biological activity, said mutein having at least one of said cysteine residues substituted by another amino acid and said mutein exhibiting the biological activity of said native protein.

Id., at 1905. The claim in *Mark* thus covers a mutant protein containing an amino acid that has been substituted for a non-essential cysteine residue. The specification at issue in that case set forth three working examples in which it was shown that each of three proteins had a non-

essential cysteine residue which could be deleted or replaced, with retention of biological activity in the resulting mutein.

The Examiner in *Mark* raised two overbreadth issues with respect to this claim: (1) whether the specification supported a claim broad enough to encompass any mutant protein and (2) whether the specification supported a claim broad enough to encompass substitution of any cysteine residue within the protein. The Examiner's reasons for rejecting the broad claim in *Mark* were as follows:

> Essentially, the position taken in the rejection is that it would require undue further experimentation to construct by recombinant methods (site specific mutagenesis) the innumerable muteins encompassed by the instant claims (claims encompass modification of any protein which comprises a "non-essential" cysteine residue) and to screen the muteins produced for any of those which exhibit biological activity after modification.

Id., at 1906. The Examiner also stated that the claims were broad enough to "encompass any protein, even those which have not been characterized or cloned." *Id.*, at 1906.

The Board of Appeals disagreed with the Examiner's analysis and concluded that the claim was enabled for all cysteine-depleted muteins of biologically active proteins in which the mutein retains the biological activity of the native protein. The Board reframed the enablement issue and reasoned that the record established that, for a given protein having cysteine residues, one skilled in the art 1) would be able to substitute for or delete the cysteine residues as desired, and 2) could routinely determine whether deletion or replacement of cysteine residues in a given instance in fact resulted in an operative mutein falling within the claims. Upon applying this framework to the specification and claims before them, the Board concluded that, although some cysteine-depleted muteins may not be operable, the disclosure was enabling for the claims, since one skilled in the art was (1) clearly enabled to perform the work that was needed to produce any given mutein falling within the description in the claims and (2) to determine whether the cysteine depleted construct retained the biological activity of the native protein.

Applying the rational of the Board in *Mark*, Applicant submits that the specification has provided sufficient teachings to enable one of skill in the art to make and use the claimed

invention without undue experimentation. Given the claims of the present invention, the specification must teach one of skill in the art how to make a vaccine according to the invention, including a description of the cytokines and antigens to be included in the vaccine. The specification must also teach what types of cells may be used to produce the vaccine composition, and how to administer the vaccine to a mammal. Lastly, the specification must teach how one of skill in the art would determine whether a mammal to which the vaccine is administered, is vaccinated according to the invention. The specification teaches the following.

1. The specification teaches on pages 16-47, more than six different families of cytokines useful in the invention, including over 80 specifically referenced cytokine molecules which may be used in vaccine compositions of the invention. These teachings include discussions of the roles of these cytokines in the immune response.

2. The specification teaches at pages 68-71, that antigens useful in the methods of the invention include **viral antigens** including hepatitis viral antigens e.g., hepatitis A, B. and C, viral components such as hepatitis C viral RNA; influenza viral antigens such as hemagglutinin and neuraminidase and other influenza viral components; measles viral antigens such as the measles virus fusion protein and other measles virus components; rubella viral antigens such as proteins E1 and E2 and other rubella virus components; rotaviral antigens such as VP7sc and other rotaviral components; cytomegaloviral antigens such as envelope glycoprotein B and other cytomegaloviral antigen components; respiratory syncytial viral antigens such as the RSV fusion protein, the M2 protein and other respiratory syncytial viral antigen components; herpes simplex viral antigens such as immediate early proteins, glycoprotein D, and other herpes simplex viral antigen components; varicella zoster viral antigens such as gpI, gpII, and other varicella zoster viral antigen components; Japanese encephalitis viral antigens such as proteins E, M-E, M-E-NS 1, NS 1, NS 1 -NS2A, 80%E, and other Japanese encephalitis viral antigen components; rabies viral antigens such as rabies glycoprotein, rabies nucleoprotein and other rabies viral antigen components; **bacterial antigens**, including pertussis bacterial antigens such as pertussis toxin, filamentous hemagglutinin, pertactin, FIM2, FIM3, adenylate cyclase and other pertussis bacterial antigen components; diptheria bacterial antigens such as diptheria toxin or toxoid and other diphtheria bacterial antigen components; tetanus bacterial antigens such as tetanus toxin or

toxoid and other tetanus bacterial antigen components; streptococcal bacterial antigens such as M proteins and other streptococcal bacterial antigen components; gram- negative bacilli bacterial antigens such as lipopolysaccharides and other gram-negative bacterial antigen components; Mycobacterium tuberculosis bacterial antigens such as mycolic acid, heat shock protein 65 (HSP65), the 30kDa major secreted protein, antigen 85A and other mycobacterial antigen components; Helicobacter pylori bacterial antigen components; pneumococcal bacterial antigens such as pneumolysin, pneumococcal capsular polysaccharides and other pneumococcal bacterial antigen components; hemophilus influenza bacterial antigens such as capsular polysaccharides and other hemophilus influenza bacterial antigen components; anthrax bacterial antigens such as anthrax protective antigen and other anthrax bacterial antigen components; rickettsiae bacterial antigens such as romps and other rickettsiae bacterial antigen component; **fungal antigens** such as candida fungal antigen components; histoplasma fungal antigens such as heat shock protein 60 (HSP60) and other histoplasma fungal antigen components; cryptococcal fungal antigens such as capsular polysaccharides and other cryptococcal fungal antigen components; coccidiodes fungal antigens such as spherule antigens and other coccidiodes fungal antigen components; and tinea fungal antigens such as trichophytin and other coccidiodes fungal antigen components; **parasite antigens** such as plasmodium falciparum antigens such as merozoite surface antigens, sporozoite surface antigens, circumsporozoite antigens, gametocyte/gamete surface antigens, blood-stage antigen pf 1 55/RESA and other plasmodial antigen components; toxoplasma antigens such as SAG-1, p30 and other toxoplasma antigen components; schistosomae antigens such as glutathione-S-transferase, paramyosin, and other schistosomal antigen components; leishmania major and other leishmaniae antigens such as gp63, lipophosphoglycan and its associated protein and other leishmanial antigen components; and trypanosoma cruzi antigens such as the 75-77kDa antigen, the 56kDa antigen and other trypanosomal antigen components; and **tumor antigens** such as telomerase components; multidrug resistance proteins such as P-glycoprotein; MAGE-1, alpha fetoprotein, carcinoembryonic antigen, mutant p53, papillomavirus antigens, gangliosides or other carbohydrate-containing components of melanoma or other tumor cells.

3. The specification teaches at page 71 to 76, methods for expressing nucleic acid molecules encoding antigens of the invention in a host cell. The specification also teaches at

page 78, lines 3-6 that a cell of the invention may already express a target antigen, and therefore need not be made to express the antigen.

4. The specification teaches at page 76-77, multiple cell types which may be used according to the invention to generate cytokine-coated cells.

5. The specification teaches at page 104-107, methods for administering the vaccine of the invention to a mammal, including methods for preparing pharmaceutical formulations, dosages, and routes of administration.

6. The specification teaches at page 82-89, **methods for determining whether an animal has been vaccinated by a vaccine composition according to the invention**. Specifically, the specification teaches that vaccination of a mammal may be determined by assays for antigen-induced T cell proliferation, assays for lymphokine-dependent cell proliferation, [^{3}H]thymidine pulse and harvest of cell cultures, immuno-enzymatic assays for cytokines using NIP- and HRPO-labeled antibodies, measuring induction of *in vivo* antibody responses to protein/polysaccharide antigens, and assays using tumor rejection. With respect to determining vaccination based on tumor rejection, the specification teaches that if survival or tumor onset in animals to which have been administered a vaccine of the invention differs from that of a control animal, then immunomodulation has been achieved.

Thus, under established law, the specification provides more than ample guidance to one of skill in the art to practice the invention according to the full scope of the claims. The specification teaches how to utilize a cytokine according to the methods of the invention and methods for determining the effectiveness of the vaccine compositions of the invention. The individual methodologies, cytokines, and molecular biological techniques described in the application for use in practicing the invention are routine in the art. Accordingly, given Applicant's teachings of the specific types of molecules to be used according to the invention, and the teachings of specific routine assays to determine whether a mammal is vaccinated by the method of the invention, provide sufficient disclosure to permit one of skill in the art to practice the invention without undue experimentation.

Testing is not undue experimentation

The Examiner has asserted that it would be undue experimentation for one of skill in the art to have to test different cytokines and cell types to determine which combination would make an effective vaccine for a particular application. Applicants submit that the legal standard on which the enablement requirement is based hinges on a determination of whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. As stated in *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ 2d 1217 (Fed. Cir. 1988), *cert denied*, 490 U.S. 1046 (1989), the court reversed the findings of the district court of undue experimentation where the specification provided only one working example. "The court ruled that since one embodiment (stainless steel electrodes) and the method to determine dose/response was set forth in the specification, the specification was enabling. The question of time and cost of such studies...failed to show undue experimentation." MPEP 2164.06 further points to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-504, 190 USPQ 214, 217-19 (CCPA 1976)), which states:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Applicants submit that, like the patent at issue in *United States v. Telectronics, Inc., supra*, the present specification teaches not only one, but many embodiments of the invention which would fall under the claims, and methods for determining whether a specific embodiment would function to vaccinate a mammal according to the claimed invention. Thus, that one of skill in the art may have to test a specific vaccine composition to determine whether it provides the particular vaccination desired does not amount to undue experimentation because the specification provides guidance in selecting the vaccine components and the tools needed to determine the effectiveness of the vaccine.

Applicant also submits that in general, with respect to the amended claims drawn to "modulating an immune response", the practitioner of the invention will already be in possession

of the antigen(s) to which he or she desires to modulate an immune response., e.g. in the form of cells containing the antigen(s). That is, the present invention (as claimed in the proposed amendments filed herewith) provides a method for modulating an immune response once cells comprising an antigen have been selected. The antigen, in the form of a cell bearing the antigen will be selected by one of skill in the art, based on their reasons for desiring to modulate the immune response. Thus, the selection of the antigen or cell to use with the method of the invention is left to the discretion of the practitioner, and for purposes of practicing the invention, the practitioner's motivation in selecting a particular antigen in the form of an antigen bearing cell is irrelevant. The present invention provides the method by which the skilled practitioner can then utilize their selected antigen-bearing cell to modulate an immune response. Applicant also reiterates, as discussed above, that operativity with respect to one (or in this case actually several) antigen in combination with a given cytokine indicates operativity for a wide range of antigens in combination with the same cytokine, since the immune system uses the same mechanisms to process antigens from disparate sources. Thus, one of skill in the art, guided by the specification, can make a determination of the particular cytokine, antigen, and cell to be used based on their own knowledge of and predictions for success for the particular type of vaccination they which to achieve, and then follow the teachings of the specification to test whether vaccination has been attained. This can be performed to the full scope of the claimed invention without undue experimentation.

Rejection of Claims 1, 2, 13, 14, 17-19, and 22-25 Under 35 U.S.C. §102(e)

Claims 1, 2, 13, 14, 17-19, and 22-25 stand rejected under 35 U.S.C. §102(e) as being anticipated by Hiserodt et al., U.S. Pat. No. 6,277,368 ("the `368 patent"). It is the Examiner's position that the `368 patent teaches a method for vaccinating a mammal using a "vaccine composition comprising a cytokine coated cell comprising an exogenous cytokine," as claimed by the Applicant. Specifically, the Examiner states in the Final Office Action mailed January 8, 2004 as follows:

> [I]t is the examiner position, that US Patent `368 teaches a method of vaccinating a mammal, including mouse, to selected antigen, comprising administering a **vaccine comprising a primary tumor cells and cytokine-secreting cells** (see

> entire document, Abstract in particular). It is noted that "**cytokine-coated cells" of the present invention are obtained by mixing cell[s] that already express an antigen, a tumor antigen for example, with engineered cytokines that can become membrane-bound** (see page 79 lines 9-25 in particular). US Patent '368 teaches that cytokines secreted by said cytokine-secreting cells are exogenous to primary tumor cells (see column 7, lines 25-40 in particular). . . . (Final Office Action , page 5, lines 22-29; bold and underlined emphasis added)

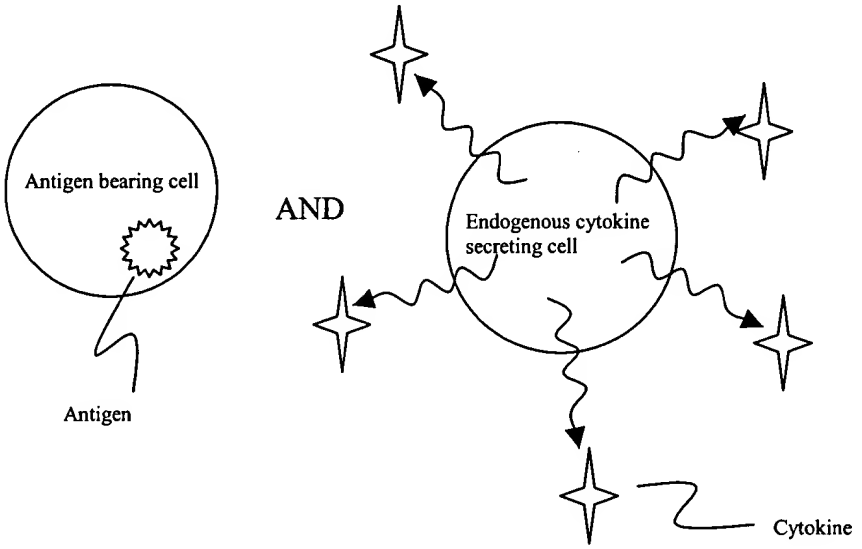
Applicant respectfully refers the Board to page 4, lines 13-16, of the specification which states that "cytokine-coated cells" are "cells which have been modified in such a manner as to bear a cell-surface associated cytokine" which "modulates the immune response in the recipient to a selected antigen or antigens contained in or attached to the [cytokine-coated] cells." Thus, the "cytokine-coated cells" of the claimed invention are modified to comprise a cell-surface associated cytokine which modulates an immune response to an antigen(s) present within or attached to the cytokine-coated cell. In other words, by the definition of cytokine-coated cell provided in the specification, **the claimed invention requires the administration of a cytokine-coated cell which (1) has been modified to contain a cytokine attached to the outer surface of the cell membrane, and (2) contains an antigen or antigens, either within or attached to its outer surface**. Thus, the cytokine-coated cell comprises the antigen and a cytokine attached to the outer surface.

Equally importantly, **the claims of the present invention further require that the cytokine attached to the cytokine-coated cell be exogenous to that cell**. The specification defines an "exogenous cytokine" as a cytokine which is "introduced from or produced outside the cell" (page 10, lines 28-29).

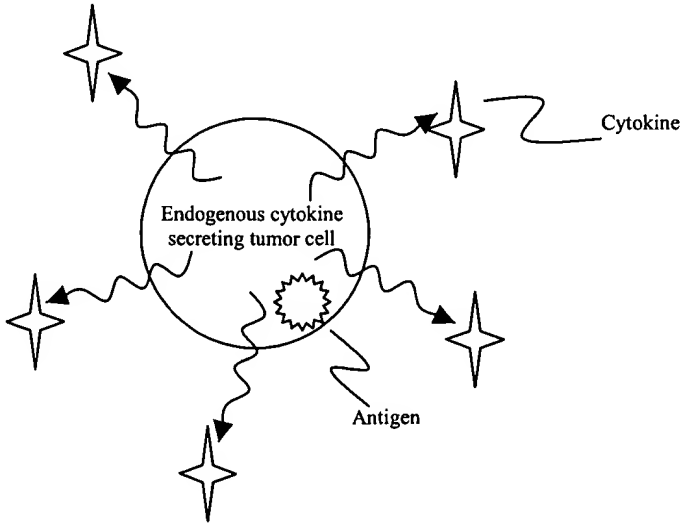
In view of the above definitions in the specification, **the claimed invention requires the use of a cytokine-coated cell which (1) has been modified to contain an cytokine attached to the outer surface of the cell membrane, wherein the cytokine is exogenous to the cell, and (2) contains an antigen or antigens, either within or attached to its outer surface.** The '368 patent cited by the Examiner neither teaches nor suggests such a cell.

More specifically, the '368 patent teaches:

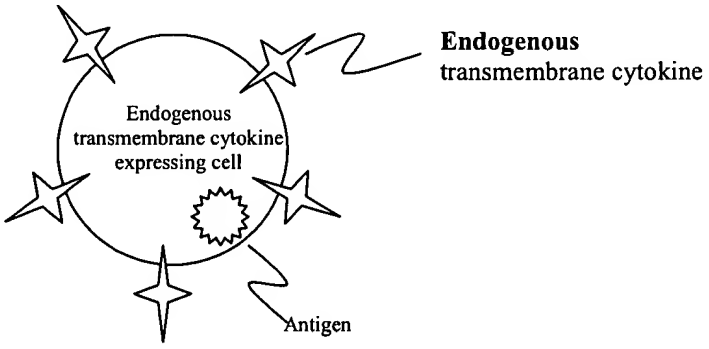
- A first cell which comprises an antigen, and a second cell which secretes an endogenous cytokine (col. 7, lines 13-17; col. 15, lines 37-41); that is the cytokine is expressed from within the cell. No cytokine is attached to the surface of the antigen-containing cell; thus, this embodiment of Hiserodt does not anticipate the instantly claimed invention.



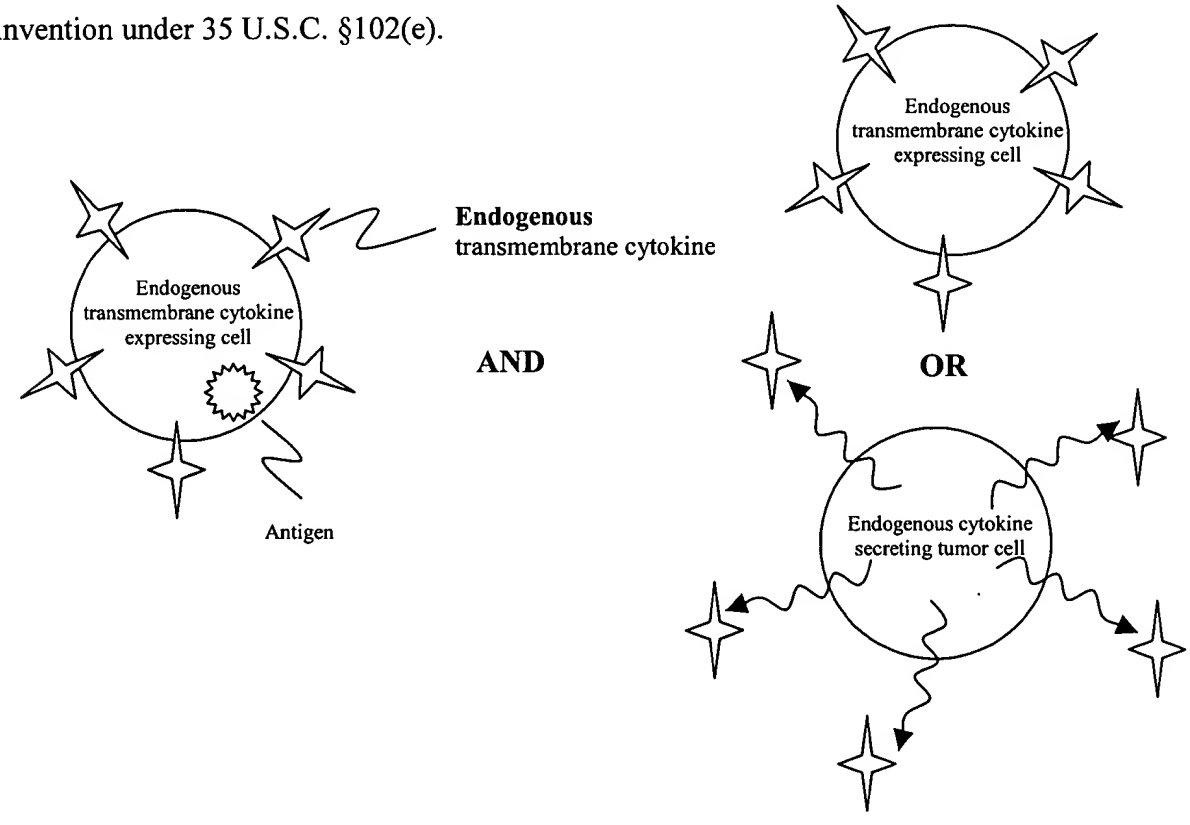
- An antigen-containing cell that is genetically modified to secrete a soluble, endogenous cytokine (col.7, lines 21-26; col. 11, lines 30-34). Again, no cytokine is attached to the surface of the antigen-containing cell; thus, this embodiment of Hiserodt does not anticipate the instantly claimed invention.



- An antigen-containing cell that is genetically modified to express an endogenous, transmembrane cytokine (col. 14, lines 57-65). Here, a cytokine is attached to the surface of the antigen-containing cell, but it is ***endogenous*** to this cell, i.e. expressed from within, rather than ***exogenous*** to it. Thus, this embodiment of Hiserodt does not anticipate the instantly claimed invention under 35 U.S.C. §102(e).



- An antigen-containing cell genetically modified to express one cytokine, admixed with a second cell genetically modified to express another cytokine (col. 11, lines 34-38). Either cytokine may be a cell-surface cytokine, but, again, Hiserodt only teaches endogenous expression by genetic modification; there is no teaching of a cytokine that is attached to the surface of the antigen-containing cell, having been added to it ***exogenously***. Thus, once again, neither this nor any embodiment of Hiserodt anticipates the instantly claimed invention under 35 U.S.C. §102(e).



In each of the embodiments taught by Hiserodt, the antigen bearing cell is administered as a vaccine where either (1) the antigen bearing cell is in combination with soluble (i.e., **NOT** membrane bound) cytokine secreted from a second cell or the antigen bearing cell, or (2) where the antigen bearing cell expresses **endogenous** membrane bound cytokine, or is administered with a second cell that expresses **endogenous** membrane bound cytokine.

Taken in view of the description of the various vaccine compositions of Hiserodt set forth above, it can be seen that none of the Hiserodt vaccine compositions anticipate the claims. It is critical to note that Hiserodt teaches that "a cytokine is referred to as a "transmembrane" protein if it normally remains stably associated in the membrane *of the cell in which it is produced*" (emphasis added; col. 13, lines 19-21). Thus, to the extent that Hiserodt teaches expression in an allogenic tumor cell of a transmembrane cytokine, this teaching is restricted to a situation in which the transmembrane cytokine is *endogenous* to the cell to which it is attached. While Applicant agrees that, in one embodiment, Hiserodt teaches an antigen bearing cell in combination with exogenous cytokine, the exogenous cytokine is secreted by another cell in the vaccine and is thus not associated with the cell surface of the antigen bearing cell to yield a cytokine coated cell as claimed in the present invention. Hiserodt does **not** teach a cell bearing an exogenous membrane bound cytokine, but teaches only an *endogenous* membrane bound cytokine. Hiserodt does teach a composition in which the antigen bearing cell is administered along with a cell producing cytokine which is exogenous to the antigen bearing cell, but this teaching is restricted to *soluble* cytokine molecules, and **not** those which would be cell-surface associated with the antigen bearing cell. Accordingly, Applicants submit that despite the various vaccine compositions taught by Hiserodt, there is no teaching of a vaccine composition in which a cytokine coated cell wherein the cytokine is exogenous to the cell is administered to a mammal to vaccinate the mammal. Applicants therefore submit that the claims are not anticipated by Hiserodt, and request that the rejection be reconsidered and withdrawn.

Rejection of Claims 3-8 and 20 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 3-8 and 20 under 35 U.S.C. §103 as being obvious over Hiserodt in view of a "Known fact" disclosed in Applicant's specification on pages 52-54

and 66-68. The Examiner asserts that Hiserodt's teachings are deficient with respect to claims 3-8 and 20 in that Hiserodt does not teach the specific types of engineered cytokine or specific opsonin-enhanced cells as recited in these claims. The Examiner asserts, however, that the "Known fact" disclosed in the specification teaches that it is conventional and within the skill of the art to produce (i) an opsonin-enhanced cell, wherein the opsonin of the cell is mannose binding protein or alpha' chain of C3b to allow more efficient binding, engulfment and internalization of the antigen; (ii) an engineered cytokine by attaching a lipid to the cytokine to permit a complex to become stably associated with the cell membrane. Applicant respectfully disagrees with the Examiner.

Applicant submits that there is no motivation to combine the teachings suggested by the Examiner. Applicant submits that the disclosure in the specification (the "known fact" asserted by the Examiner) that the technology existed to link a lipid moiety to a cytokine molecule, or to employ an opsonin to enhance binding and engulfment does not equate to a teaching that such a modification is obvious for purposes of immunizing an animal. Where in Hiserodt and/or the known fact does one find the suggestion to combine a cytokine-coated cell with an opsonin or lipid moiety as claimed in claims 3-8? The level of skill in the art (e.g., the technique for modifying a cytokine to include a lipid) cannot be relied upon to provide the suggestion to combine references (*Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308 (Fed. Cir. 1999), particularly when the instant invention claims elements that are novel over the prior art. The Examiner asserts that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. Provided that it takes in to account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper (citing *In re McLaughlin*, 170 USPQ 209 (CCPA1971)). This is exactly the basis on which the Examiner's obviousness rejection is flawed. The rejection is based on knowledge gleaned only from the Applicant's disclosure; that is, the novel disclosure of methods for vaccinating or modulating an immune response to an antigen using cytokine coated cells comprising exogenous cytokine.

The "Known fact" referred to by the Examiner, that such an engineered cytokine could be used according to the methods of the invention to vaccinate a mammal against an antigen, and that the vaccine composition may be combined with an opsonin is a teaching which is unique to the present specification. The combination of a cytokine coated cell and an opsonin, as claimed in the invention, is not a "known fact". It is the combination on which the invention is based; immunization with cytokine-coated cells bearing an exogenous cytokine had never existed prior to the instant invention. The law is clear that taking the teachings of the present invention relating to the claimed method and attempting to fill in the gaps in the prior art with such teachings amounts to hindsight reconstruction of the invention, and is not permitted. Applicant submits that to establish the motivation to combine the "Known fact" with Applicant's novel teachings of a cytokine coated cell, "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed" (emphasis added) *In re Kotzab,* 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). Applicant submits that since, as described above with respect to the Examiner's mistaken rejection under 35 U.S.C. §102(e), Hiserodt et al. does not teach the claimed invention, the Examiner has not met this burden of demonstrating why one of skill in the art, with no knowledge of Applicant's invention, would have been motivated to make the suggested combination. Without the requisite motivation, there can be no finding of obviousness.

The law is clear that "[i]t is impermissible . . . simply to engage in a hindsight reconstruction of the claimed invention...The references themselves must provide some teaching whereby the Applicant's combination would have been obvious." (*In re Gorman*, 18 U.S.P.Q.2d 1885, 1888 (Fed. Cir. 1991)). In addition, it has long been recognized that a novel combination of elements, not previously combined in the same way by the prior art can be patentable regardless of whether a specific element is disclosed in the art. *Kesling v. General Motors Corporation.* 66 F.Supp.1 (1946). The methods of vaccinating an animal against an antigen using a vaccine composition comprising a cytokine-coated cell as claimed is novel and non-obvious over the prior art.

The Examiner has argued that it was well known in the art that an immune response to an antigen could be enhanced by coupling the antigen to an opsonin. Relying on this, the Examiner has argued that one of skill in the art would have been motivated to combine the cytokine-coated cell vaccine composition of the invention with an opsonin to enhance binding and engulfment. The flaw in this argument is that the Examiner is trying to combine a known element with a novel invention to render the invention obvious. Applicants submit that the combination of an alleged obvious variant of a novel invention cannot render the invention as a whole obvious, because the combination of a novel invention and an alleged obvious variation is necessarily non-obvious. In other words, the combination of Hiserodt and the "Known fact" does not teach each element of the claimed invention as required for a finding of obviousness. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). How could it be obvious to one of skill in the art to combine, for purposes of immunization, an opsonin with the exogenous cytokine coated cells of the invention, when immunization with the cytokine coated cells of the invention had never been described outside of the present application? The motivation to combine the references cited by the Examiner is gleaned only from Applicant's own disclosure of the invention, and is thus an impermissible hindsight reconstruction of the claimed invention (*In re McLaughlin*, 443 F.2d 1392 (CCPA 1971)).

Applicant therefore submits that the present invention is not obvious over Hiserodt in view of Applicant's own disclosure, and request that the rejection be reconsidered and withdrawn.

Conclusion

It is respectfully requested that the rejections be reversed and that the claims be allowed. This Brief is being filed in triplicate.

Respectfully submitted,

(34,614)

Date: June 25, 2004

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Appendix I

1. A method of vaccinating a mammal to a selected antigen, the method comprising

administering to a mammal a vaccine composition comprising a cytokine-coated cell comprising said selected antigen, wherein said cytokine of said cytokine-coated cell is exogenous to said cell, and wherein said mammal is vaccinated to said selected antigen.

2. A method of vaccinating a mammal to a selected antigen, the method comprising

administering to a mammal a vaccine composition comprising a cytokine-coated cell, wherein said cytokine of said cytokine-coated cell is exogenous to said cell, wherein said cytokine-coated cell comprises said selected antigen and is admixed with an engineered cytokine, and wherein said mammal is vaccinated to said selected antigen.

3. The method of claim 1 or claim 2 wherein said vaccine composition further comprises an opsonin-enhanced cell.

4. The method of claim 3 wherein said opsonin of said opsonin-enhanced cell is selected from the group consisting of mannose binding protein or the alpha' chain of C3b.

5. The method of any one of claims 1 or 2 wherein said cytokine of said cytokine-coated cell comprises a lipid.

6. The method of claim 5 wherein said cytokine comprises a GPI moiety.

7. The method of claim 5 wherein said cytokine comprises a fatty acid.

8. The method of claim 7 wherein said fatty acid is palmitate.

13. A method of vaccinating a mammal to a selected antigen, the method comprising administering to the mammal a vaccine composition comprising a cytokine-coated cell, , wherein said cytokine of said cytokine-coated cell is exogenous to said cell, wherein said cytokine is a ligand for the GM-CSF receptor, and wherein said mammal is vaccinated to said selected antigen.

14. The method of claim 13, wherein said ligand for the GM-CSF receptor is GM-CSF.

15. A method of vaccinating a mammal to a selected antigen, the method comprising; administering to a mammal a vaccine composition comprising a cytokine-coated cell, , wherein said cytokine of said cytokine-coated cell is exogenous to said cell, wherein said cytokine is a ligand for one of the following receptors: the IL-2 receptor, the IL-4 receptor, the IL-6 receptor, the IL-10 receptor, the IL-12 receptor, the TNF-α receptor, the IFN-γ receptor, a chemokine receptor.

16. The method of claim 15, wherein said ligand is selected from the group consisting of: IL-2, IL-4, IL-6, IL-10, IL-12, TNF-α, IFN-γ, or a chemokine.

17. The method of any one of claims 1 or 13, wherein said cell of said cytokine-coated cell is a pathogenic cell.

18. The method of claim 17 wherein said pathogenic cell is a malignant tumor cell.

19. The method of claim 17 wherein said cell of said pathogenic cell is selected from the group consisting of: a bacterium, a virus, a fungus, a cell of a parasite.

20. The method of claim 17, wherein said vaccine composition further comprises an opsonin-enhanced pathogenic cell.

22. The method of any one of claims 1 or 13, wherein said cytokine-coated cell is substantially unable to divide in vitro.

23. The method of any one of claims 1 or 13, wherein said vaccine composition is attenuated.

24. The method of any one of claims 1 or 13, wherein said cytokine is an antitumor cytokine.

25. The method of any one of claims 1 or 13, wherein said cytokine is extremely bioactive, natively bioactive, or suprabioactive.